

REMARKS

Claims 25, 28 and 31 have been amended to include structural characteristics of the α_1 subunit of the T-type channel. Support for these structural parameters - hybridization under specified conditions to SEQ. ID. NO: 23, 25 or 27 is found on page 22 of the specification, lines 12-20. SEQ. ID. NO's: 23, 25 and 27 represent full-length mammalian α_1 T-subunits. The definition of activation simply makes explicit the inherent meaning of "activation". No new matter has been added and entry of the amendment is respectfully requested.

The Rejection Under 35 U.S.C. § 112, Second Paragraph

The first portion of this rejection is addressed by amendment. The Office states that the name " α_1 subunit of a mammalian T-type calcium channel" is not sufficient to characterize, structurally, the subunit itself. This has been remedied by requiring that, in addition to the requirement that the α_1 subunit be functional as a T-type channel, the subunit must be encoded by a nucleotide sequence that hybridizes under specified conditions to the full-length α_1 sequences set forth in SEQ. ID. NO's: 23, 25, and 27. Accordingly, this aspect of the rejection may be withdrawn.

The second part of this rejection relates to claims 25-27; again, an amendment has been made to clarify that what is measured is the influx of calcium ions into the cell. As the Office is surely aware, there are a number of methodologies well-known in the art to make such measurements. The method using the "gold standard" patch clamp reading is described on pages 25-26 of the specification; alternatively, more facile measures permitting high throughput is referred to on page 22 - *i.e.*, the use of radiolabeled ^{45}Ca uptake or measuring calcium uptake by inclusion of calcium ion-sensitive fluorescent dyes within the cells. Those of ordinary skill in the art are well aware of how to measure activation of calcium ion channels by measuring the enhanced influx of calcium ions. There is no need to specify a particular method choice, among many available, in the claims. As the Office is also aware, it is not the function of the claims to teach how to perform the invention; rather to define its metes and bounds. Claims 25 -27 clearly do exactly that.

It appears that the rejection of claim 28, also included in this regard, can be withdrawn for the same reasons as those set forth above.

Claim 31 is rejected on the basis of the assertion that compound may bind to the α_1 subunit and be neither antagonist or agonist. Respectfully, applicants disagree. If the compound binds to the channel, and fails to activate it, it will prevent other compounds which are able to activate the channel from binding and is therefore an antagonist. If compounds do activate the channel when they bind, they are agonists. It is conceivable, of course, that a compound could bind a channel in such a way that it does not compete with binding of true agonists. However, this would be expected to be relatively rare. And in any event, this is addressed by the amendment to claim 31 which requires that the binding is determined by observing competitive binding with an agonist or antagonist.

Claim 32 is said to be indefinite because it is not clear how the determination of competitive binding determines if a compound is an agonist or antagonist. This has been explained above. If the compound binds and activates the channel it is an agonist; if it binds in a way so as to preclude the binding of known agonists or antagonists, but does not activate the channel, it is an antagonist. It must be one or the other. The claim does not require that the agonist be distinguished from the antagonist; only that the compound is identified as one or the other. It is a simple matter, once this screening is done, to verify which of these two simple alternatives is the case; no undue experimentation is required.

Rejection of claim 33 is obviated by its cancellation.

Finally, the Office states that "just measuring one effect without correlation with a standard will not produce the results required by the methods claim." This apparently is the basis for rejection of all of claims 25-33. Respectfully, applicants fail to understand this basis for rejection. It is unclear what "standards" the Office is requiring. If the cell is sitting there with its calcium ion channel displayed in a pool of radioactive calcium ions and contacting the cell with a compound to be tested suddenly causes the cell to become labeled with the radioactive calcium ions, it seems pretty clear that the compound is causing uptake of calcium ion and is an agonist.

If, now, another compound is added and the uptake of radioactive calcium ceases or is slowed down, the newly added compound is an antagonist. What kind of standard has to be applied other than this? Further explanation of this basis of rejection is requested in order for applicants further to respond.

The Rejections Under 35 U.S.C. §§ 101 and 112, First Paragraph

The basis for this rejection can be stated very simply. The Office takes the view that the invention as claimed does not have a real world utility that is substantial and specific. There is no dispute on the part of applicants that a substantial and specific utility for the invention as claimed must be shown or understood in the art. Applicants' disagreement is with respect to whether this is the case.

First, the Office appears to misinterpret what is being claimed. As part of the rejection, the Office states that "neither the specification or the art of record disclose any disease states treatable by the novel polynucleotides of instant invention or polypeptides encoded by them." That is not the invention claimed. Rather, the invention claimed is a method to identify agonists and antagonists of the calcium ion channels made available to the art by the present invention. Applicants have never asserted that the channels themselves or the nucleotides encoding them are candidates as pharmaceuticals for treating any disease. Rather, as is well understood by practitioners, it is the agonists or antagonists of these channels which have an effect on the activity of the endogenous calcium ion channels in a subject to be treated. The channels themselves and the nucleic acids containing nucleotide sequences encoding them are research and screening tools to identify such agonists and antagonists.

While *Brenner v. Manson* clearly requires a utility other than simply finding out what the claimed subject matter is good for, it does not preclude a patenting of research tools or screening tools and a multiplicity of such tools have been patented, as the Office surely understands.

So, the real question is: What are the conditions that are treatable by the agonists or antagonists that would be identified by the presently claimed methods?

For starters, these conditions are identified in the specification as epilepsy, migraine, ataxia, schizophrenia, hypertension, arrhythmia, angina, depression, small lung carcinoma, Lambert-Eton Syndrome, and Parkinson's disease. Perhaps this seems too long a list. However, the Office is reminded that calcium ion traffic is a fundamental influence on the behavior of a multiplicity of cells, so it should not be surprising that a fairly large number of conditions are suitable targets for treatment by regulating calcium ion flow using the agonists and antagonists identified by the methods of the invention.

As stated in Dr. Snutch's declaration, "abnormal T-type activity is associated with a number of cardiac conditions, with hypertension, with neurological diseases including spastic convulsions and with impaired fertility. An antagonist identified with regard to any T-type channel would be useful in all of these conditions." The Office has adduced no independent evidence to contradict the sworn statement of Dr. Snutch, an expert in this field. The Office has offered only its own opinion, which, respectfully, is not adequate to rebut this sworn testimony.

Finally, respectfully, the Office appears to have ignored the precedent that at least two patents have issued directed to nucleotide sequences encoding T-type channels: U.S. 6,358,706 and U.S. 6,309, 858. Obviously the art itself understands that T-type channels are useful; as claimed presently, they are useful for identifying agonists and antagonists of their activity which are in turn useful in treating a large number of conditions. This is exactly the same thing that is stated by the patentees in these issued patents. See, for example, column 6, lines 33-50, in the '706 patent and column 19, lines 53-57, of the '858 patent.

In addition, an entire litany of patents have been issued by the Office with respect to N-type calcium ion channels based on the same logic that applicants have been asserting in the present application. The Office may be familiar with the many patents issued to Sibia on various components of the N-type channels (no one subunit of which, by the way, is functional by itself). These include, for example, U.S. 6,096,514; U.S. 6,090,623; U.S. 6,013,474; U.S. 5,876,958; and at least ten more.

Applicants are indeed puzzled as to the position of the Office in this particular case since the utility of calcium ion channels in general as screening tools for therapeutics useful in a variety of diseases is so well established in the art. That is why such considerable effort has been focused on obtaining the nucleotide sequences encoding these channels--simply to permit the claimed methods herein to be performed in order to identify agonists and antagonists.

For the reasons stated above, this basis for rejection may properly be withdrawn.

CONCLUSION

Claims 25-31 remain pending. The claims now recite structural characteristics of the functional T-type channels used in the methods claimed. It has been pointed out that determining the activation of calcium ion channels can be done by a variety of methods, all of which are well understood in the art and these, by law, need not be specified in the claims. Finally, the specification recites and the art recognizes the utility of the claimed methods in identifying compounds in treating a variety of conditions. Accordingly, it is believed that claims 25-31 is in a position for allowance and passage of these claims issued is respectfully requested.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 381092000720.

Respectfully submitted,

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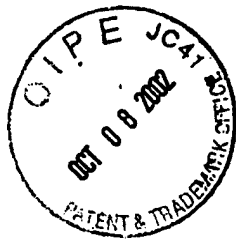


EXHIBIT A. - VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

25. (Amended) A method to identify a compound which behaves as an agonist for a T-type [mammalian] calcium channel which method comprises:

a) contacting a recombinant cell which expresses the α_1 subunit of a heterologous [mammalian] T-type calcium channel with a compound to be tested; and

b) determining the ability of said compound to activate said α_1 subunit;
wherein said α_1 subunit is functional as a T-type calcium ion channel and is encoded by a nucleotide sequence which hybridizes under conditions of stringency corresponding to washing at 62° C in 0.2 x SSPE/0.1% SDS to a nucleic acid comprising SEQ. ID. NO: 23, 25 or 27, and

wherein said activating comprises enhancing the flow of calcium ions into said cell in the presence as compared to the absence of said compound;

whereby a compound which activates said α_1 subunit is identified as an agonist of said T-type calcium channel.

27. (Amended) The method of claim 25, wherein said cells contain a fluorescent dye sensitive to intracellular calcium concentration and said activation is determined by observing a change in the fluorescence of said dye when said contacting is performed.

28. (Amended) A method to identify an antagonist of a T-type calcium channel which method comprises:

a) contacting a recombinant cell expressing the α_1 subunit of a heterologous [mammalian] T-type calcium channel with a known agonist of said T-type calcium channel;

b) contacting said cell with a compound to be tested; and

c) determining the ability of said compound to diminish the activation of said α_1 subunit by said agonist;

wherein said α_1 subunit is functional as a T-type calcium ion channel and is encoded by a nucleotide sequence which hybridizes under conditions of stringency

corresponding to washing at 62° C in 0.2 x SSPE/0.1% SDS to a nucleic acid comprising SEQ. ID. NO: 23, 25 or 27, and

wherein said activating comprises enhancing the flow of calcium ions into said cell in the presence as compared to the absence of said agonist;

whereby a compound which diminishes the activation of said α_1 subunit by said agonist is identified as an antagonist.

30. (Amended) The method of claim 28, wherein said cells contain a fluorescent dye sensitive to intracellular calcium concentration and said activation is determined by observing a change in the fluorescence of said dye when said contacting is performed.

31. (Amended) A method to prescreen compounds as agonists or antagonists of T-type calcium ion channels by virtue of their ability to bind said T-type channels which method comprises:

- a) contacting a recombinant cell expressing the α_1 subunit of a heterologous T-type calcium channel with a compound to be tested; and
- b) determining the ability of said compound to bind to said cell expressing said α_1 subunit;

wherein said binding is determined by observing competitive binding with a known agonist or antagonist of said channel;

wherein said α_1 subunit is functional as a T-type calcium ion channel and is encoded by a nucleotide sequence which hybridizes under conditions of stringency corresponding to washing at 62°C in 0.2 x SSPE/0.1% SDS to a nucleic acid comprising SEQ. ID. NO: 23, 25 or 27,

whereby a compound which is determined to bind said cell is identified as a compound which will behave as either an agonist or antagonist of a T-type calcium channel.